REMARKS

Claims 1-6, 12, 13, and 16 are currently pending on the merits and under examination. Claims 7-11, 14, and 17-21 have been withdrawn without prejudice. Claim 15 has been canceled without disclaimer or prejudice. Applicants reserve the right to file one or more continuation or divisional applications to any withdrawn or canceled subject matter. No new matter has been added by this amendment.

I. Rejection under 35 U.S.C. § 101

Claims 1-6, 12, 13, and 16 are rejected under 35 U.S.C. § 101 for lacking support for a specific and substantial asserted utility or a well-established utility on pages 4-9 of the office action. Specifically, the Examiner alleges that there is no direct evidence that the polypeptide of SEQ ID No. 7 is produced. Moreover, it is alleged that the specification provides no well-established utility for the new, uncharacterized LAPTM4B polynucleotides of SEQ ID Nos. The Examiner further argues that the correlation of the amplification of genomic DNA with the amplification of mRNA and the correlation of the amplification of mRNA with the amplification of polypeptide are not established in the art (*see* pages 5-6 of the office action). Accordingly, the Examiner contends that the poor correlation between mRNA expression and protein abundance in normal tissues renders the functional significance of LAPTM4B genomic DNAs and polypeptides unpredictable in the complicated human tumors. Therefore, the Examiner concludes that the claimed polynucleotides and encoded polypeptides need further research to establish substantial practical use.

Applicants respectfully traverse the rejection. Applicants respectfully submit that the claimed invention does have a specific and substantial asserted utility as disclosed in and supported by the specification for the following reasons.

As stated in MPEP 2107.02.:

> [t]here is no predetermined amount or character of evidence that must be provided by an applicant to support an asserted utility, therapeutic or otherwise. Rather, the character and amount of evidence needed to support an asserted utility will vary depending on what is claimed (*Ex parte Ferguson*, 117 USPQ 229 (Bd. App. 1957)), and whether the asserted utility appears to contravene established scientific principles and beliefs. *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967); *In re Chilowsky*, 229 F.2d 457, 462, 108 USPQ 321, 325 (CCPA 1956).

> Furthermore, the applicant does not have to provide evidence sufficient to establish that an asserted utility is true 'beyond a reasonable doubt.' *In re Irons,* 340 F.2d 974, 978, 144 USPQ 351, 354 (CCPA 1965). Nor must an applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty. *Nelson v. Bowler*, 626 F.2d 853, 856-57, 206 USPQ 881, 883-84 (CCPA 1980) (reversing the Board and rejecting Bowler's arguments that the evidence of utility was statistically insignificant. The court pointed out that a rigorous correlation is not necessary when the test is reasonably predictive of the response). *See also Rey-Bellet v. Englehardt*, 493 F.2d 1380, 181 USPQ 453 (CCPA 1974) (data from animal testing is relevant to asserted human therapeutic utility if there is a "satisfactory correlation between the effect on the animal and that ultimately observed in human beings"). Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true.

A. Peptides Encoding The Claimed Sequences Be Produced And Identified

Applicants respectfully bring to the Examiner's attention that it is within the capacity of a skilled artisan to use the disclosed nucleotide sequences of SEQ ID Nos: 1-3, 6 and 8 to produce the polypeptides having the amino acid sequences of SEQ ID Nos: 4 and 7. The specification discloses SEQ ID No: 1 is an intact open reading frame encoding the amino acids sequences of SEQ ID No: 4 (*see* page 2, lines 9-11 in the specification). SEQ ID Nos: 2 and 3 are two full length cDNAs of LAPTM4B with alternative tailing signals, which contain the same ORF as SEQ ID No: 1 (*see* page 2, lines 14-18 in the specification). Therefore, the polypeptides encoded by SEQ ID Nos: 2 and 3 will be the same as that of SEQ ID No: 1. SEQ ID No: 6 is an allelic gene of SEQ ID No: 1 (*see* page 2, line 27 to page 3, line 8 of the specification). SEQ ID Nos: 1-3 and 6 are also referred to as LAPTM4B *1 and *2, respectively. (*Please see* the amendment filed on February 12, 2008). SEQ ID No: 8 is the promoter sequence of LAPTM4B gene. It is well known in the art that nucleic acid molecules having the nucleotide sequences thereof and polypeptides encoded therewith can be produced using the said nucleic acid molecules.

Accordingly, a one of ordinary skill in the art is able to use the nucleic acid molecules having the nucleotide sequence SEQ ID Nos: 1-3, 6 and 8 to prepare polypeptides having the amino acid sequence of SEQ ID Nos: 4 and 7 and to derive DNA and RNA molecules that can be used as primers and probes in PCR, Southern blot, Northern blot, etc. and as shRNA or siRNA in RNAi.

B. LAPTM4B Has Specific And Substantial Utility

LAPTM4B has been demonstrated to play pivotal roles in tumorigenesis, tumor growth and metastasis in the instant invention. The specification discloses that both mRNA level and the LAPTM4B-35 protein level of LAPTM4B are up-regulated in the majority of hepatocellular carcinoma tissues by experiments, such as, Northern Blot (*see* Fig. 1A) and *in situ* hybridization for mRNA (Fig. 2A), and immuno-histochemistry (*see* Fig. 2B), immuno-cytochemistry. ((*See* Fig. 2C) and Western Blot (*see* Fig. 3) for protein (*see* page 3, line 30 to page 4, line 2; Shao *et al.* Oncogene., 2003, 22(32): 5060-5069; Liu *et al.* World J. Gastroenterol. 2004, 10(11): 1555-1559; Peng *et al.* World J. Gastroenterol. 2005, 11(18): 2704-2708). The upregulated LAPTM4E-35 protein level is related with many cancers and its magnitude is positively correlated with hapatocellular carcinoma grades and negatively correlated with hapatocellular carcinoma differentiation, implicating the close relationship between LAPTM4B and HCC. (*See* page 4, lines 12-16, 16-28 and Fig. 1C and Fig. 17; *see also* Shao et al. Oncogene., 2003, 22(32): 5060-5069; Peng *et al.* World J. Gastroenterol. 2005, 11(18): 2704-2708; Zhou et al. European Journal of Cancer, 43 (4): 809 – 815; Zhou et al. Cancer Letter, 264(2): 209-217; Yang *et al.* Oncology Reports, 2008, July, accepted). Furthermore, the inventors have recently demonstrated that the high level of LAPTM4B-35 in HCC is also correlated positively with the presence of tumor thrombin in portal vein (metastasis in liver) and adversely with the survival period (prepared manuscript to Hepatology). Therefore, the correlation between the up-regulation of LAPTM4B and clinical malignance of patients with HCC and some other cancers indicates the specific and substantial utility of LAPTM4B as a novel marker in cancer diagnosis and prognosis. For example, primers and probes having a segment of the nucleotide sequence of SEQ ID Nos: 1-3, 6 and 8, and antibodies directed to LAPTM4B polypeptides can be utilized to determine its expressive level in the biological samples (*see* Fig. 8, Shao et al. Oncogene., 2003, 22(32): 5060-5069; Liu et al. World J. Gastroenterol. 2004, 10(11): 1555-1559; Peng et al. World J. Gastroenterol. 2005, 11(18): 2704-2708; Zhou et al. European Journal of Cancer, 43 (4): 809 – 815; Zhou et al. Cancer Letter, 264(2): 209-217; Yang et al. Oncology Reports, 2008, July, accepted; and also unpublished data in the inventor's lab). These applications would be significant in the diagnosis of cancers, monitoring of cancer progression and evaluation of prognosis (*see* page 24, lines 29-33 and Fig. 8).

Additionally, cell-based assays confirmed that over-expression of LAPTM4B-35 in the transfected cells induced uncontrolled cell proliferation and inoculation of the transfected cells elicit tumorigenesis in xenografts (*see* Fig. 4-7, page 6, lines 3-13; *see also* He et al. J. Peking University (Health Sciences), 2003, 35(4): 348-352; Zhou et al. Falk Symposium 150, Berlin, 2005.10, Abstract p.121 and poster prized by the conference; Zhou et al. The 3rd International Congress of Cancer progression, Baltimore, 2006, Abstract, p.102-103 and poster). The inventor's subsequent study also demonstrates that up-regulation of LAPTM4B-35 elicits in nude mice the tumorigenesis with strong invasiveness of human liver L02 cell transfected with LAPTM4B and up-regulative expressing LAPTM4E3-35 (*see* Zhou et al. Falk Symposium 150, Berlin, 2005.10, Abstract p.121 and poster prized by the conference; Zhou et al. The 3rd International Congress of Cancer progression, Baltimore, 2006, Abstract, p.102-103 and poster). Furthermore, the over-expression of LAPTM4B promotes the up-regulation of some proto-oncogenes (c-myc, c-fos, c-jun, *etc.*) and cell cycle promoting proteins (cyclin D1 and cyclin E), and the downregulation of some tumor suppressor genes as the activation of signaling pathways (*see* page 6, lines 30-33, Fig. 13-16; *see also* He et al. J. Peking University (Health Sciences), 2003, 35(4): 348-352; Zhou et al. Falk Symposium 150, Berlin, 2005.10, Abstract p.121 and poster prized by the conference; Zhou et al. The 3rd International Congress of Cancer progression, Baltimore, 2006, Abstract, p.102-103 and poster; Zhou et al. The 5th Asian-Pacific Organization for Cell Biology Congress, 2006, Beijing, Abstract, p.77, oral presentation; Zhou et al. The 9th Conference of Chinese Society for Cell Biology, Abstract p.52, 2007, Guangzhou, oral presentation). This evidence proves that overexpression of LAPTM4B induces a series of molecular alterations, which contribute to deregulation of cell proliferation, the most common and pivotal characteristics of malignant transformation and tumorigenesis, and to enhancement of migration and invasion, the most important cellular phenotype of metastasis (*see* Hanahan et al. Cell, 2000, 100(1): 57-70). Therefore, LAPTM4B can be utilized as targets in therapy of cancers through RNAi direct to LAPTM4B-35 mRNA, DNA vaccine, peptide vaccine, specific antibodies and chemical inhibitors to the signaling pathway involved. (*See* page 25 in the specification).

In another aspect, the specification discloses a significant difference in the frequencies of genotype LAPTM4B*2/2 between patients with HCC and the controls but no difference in the frequencies of LAPTM4B genotypes in patients with esophagus carcinoma and recto cancer.

(*See* Table 2, pages 21-23, Table 4, page 23; Deng *et al.* Beijing Da Xue Xue Bao, 2005, 37(3):302-305; Liu *et al.* Ann. Oncol., 2007, 18(2): 311-316; Cheng *et al.* Ann. Oncol., 2008, 19(3): 527-532). This evidence indicates that allele *2 may contribute to a novel criterion for screening individuals in the high-risk population who are susceptible to specific cancers. Thus the sequences of primers (E2 and R2), which are included in SEQ ID No: 6 and disclosed in the in the present invention, can be used in PCR as a novel marker to screen the susceptible individuals form the high-risk population of specific cancers. This screening is significant for preventing the susceptible individuals from suffering from related cancers because tumorigenesis depends on both genetic factors and environmental factors. In addition, the DNA vaccine (SEQ ID Nos: 1-3) and peptide (SEQ ID No: 4 and/or 7) vaccine may prevent the susceptible individuals from suffering from related cancer.

In summary, the specification as filed has established the specific and substantial utility of LAPTM4B in tumorigenesis, tumor growth and metastasis, which has been confirmed in the inventor's subsequent research.

C. Single gene as a target in cancer therapy

Applicants respectfully bring to the Examiner's attention that it is well known in the art that the activation or deactivation of a key oncogene can play a pivotal role in tumorigenesis and progression or regression in spite of the complexity and heterogeneity of the human tumors, numerous pathways and different genome-scale global profiling. For example, a number of articles have revealed that c-myc is activated in a large number of human cancers; sustained high level of Myc can result in oncogenic activation and contribute to progress of a wide range of human cancers. (*See* Shachaf et al. Nature, 2004, 431(7012): 1112-1117). On the other hand, "inactivation of the MYC oncogene is sufficient to induce sustained regression of invasive liver cancers. MYC inactivation resulted en masse in tumor cells differentiating into hepatocytes and biliery cells forming bile duct structures; whereas myc reactivation immediately restored their neoplastic features" (*see* Arvanitis et al. Seminars in Cancer Biology, 16 (2006): 313-317). The present application discloses that upregulation/activation of LAPTM4B mRNA and LAPTM4B-35 not only activates multiple oncogenes and proliferation-promoting proteins which involve in tumorigenesis triggered by LAPTM4B, but also can markedly induce constitutive activation of c-Myc (*see* page 6, lines 30-33 and Fig. 13C), indicating that LAPTM4B works upstream of c-

myc. Therefore, it is reasonable to conclude that the strategies directed to LAPTM4B single gene may produce efficacy on cancer suppression.

II. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-6, 13, and 14 are rejected under 35 U.S.C. § 112, first paragraph, for lacking support of a specific or substantial asserted utility or a well established utility.

For the reasons discussed above, it is respectfully requested that this rejection of claims 1-6, 13, and 14 under 35 U.S.C. § 112, first paragraph, be withdrawn.

III. Conclusion

The foregoing amendments and remarks are being made to place the application in condition for allowance. Applicants respectfully request entry of the amendments, reconsideration and the timely allowance of the pending claims. Should the Examiner find that an interview would be helpful to further prosecution of this application, the Examiner is invited to telephone the undersigned at their convenience.

If there are any additional fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0310.

Dated: **November 10, 2008**
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